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Systemic therapies for severe atopic dermatitis in children and adults

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Activity Objectives

1. To be able to list common reasons why standard topical treatment might fail in patients with severe atopic dermatitis (AD).
2. To have an understanding of the current evidence for the use of systemic immunosuppressive drugs in patients with severe AD.
3. To be familiar with the recommended investigations before starting and during treatment with cyclosporine, azathioprine, and methotrexate.
4. To be able to list important short-term and potential long-term side effects of cyclosporine, azathioprine, and methotrexate.

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CLINICAL VIGNETTE

A 12-year-old boy was referred to a tertiary pediatric dermatology center with a lifelong history of severe atopic dermatitis (AD) (see Fig E1 in this article's Online Repository at www.jacionline.org). He had lately missed several weeks of school because of hospital admissions for recurrent skin infections, lack of sleep, and intense discomfort. Over the years, he had primarily been taking regular emollients and potent topical steroids and, more recently, underwent a failed trial of UV phototherapy. Intense topical steroid therapies, wet wraps with emollient overnight, after-treatment education on the day ward, and a prolonged course on oral antibiotics did not result in sustained improvement. The history did not suggest any contributory immediate or delayed allergies, and results of skin prick tests to a broad range of food allergens and aeroallergens, as well as patch tests to a range of relevant allergens, were negative.

Because of the severity of his disease (SCORAD score, 60/103; Children's Dermatology Life Quality Index [CDLQI] score, 28/30), he was started on cyclosporine. A dose of up to 5 mg/kg/d somewhat decreased disease severity over a 12-week period, but his quality of life was still significantly affected (SCORAD score decreased to 32 and CDLQI score decreased to 18). Our patient was subsequently switched to azathioprine at 3 mg/kg/d in 2 divided doses, with no significant clinical benefit after 3 months. Finally, he was started on methotrexate at a treatment dose of 0.4 mg/kg/wk. Folic acid was also administered (5 mg daily except the day of his methotrexate dose); 12 weeks later, his skin inflammation had settled (SCORAD score, 10; CDLQI score, 4), and he had missed no days off school in 4 weeks. At review after 6 months, he remained well and was using minimal topical therapies. His SCORAD score continued to be low at 8, and his CDLQI score was 3.

The full version of this article, including a review of relevant issues to be considered, can be found online at www.jacionline.org. If you wish to receive CME or MOC credit for the article, please see the instructions above.

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REVIEW

Severe AD has a very significant effect on the quality of life of the affected patient and, in children, on the family unit, posing a considerable therapeutic challenge to the physician, as illustrated in this case report. In general, mild-to-moderate AD can be adequately controlled with topical therapy, UV therapy, or both. However, a subset of children and adults with severe or recalcitrant disease require systemic immunosuppression to induce and maintain disease control.[E1]

What is severe AD?

There is no universally agreed on definition of severe AD. From a clinical point of view, severe disease can be thought of as AD that is resistant to potent topical corticosteroid or calcineurin inhibitor and UV therapy and that is associated with a considerable effect on quality of life. The European Academy of Dermatology and Venereology Taskforce on AD defined severe disease as a SCORAD severity score of greater than 40, but this definition is not very helpful when faced with a case in the clinic, where the decision to start immunosuppressive treatment is not only guided by disease severity but also the impairment of the patient's quality of life, such as with regard to sleep disturbance and effect on schooling.[E2]

Using systemic immunosuppressive drugs in children and adults with severe AD

Before considering starting a child or adult on an immunosuppressive drug, it is important to identify potential triggers, such as irritants, and exacerbating factors, such as immediate and delayed hypersensitivity, through allergy testing (skin prick testing, specific IgE measurement, and patch testing).[E3] In addition, reasons why topical treatments have failed need to be taken into account. Applying creams and ointments is labor intensive and time consuming. Patient education on their use has a proved additional benefit with regard to both disease severity and quality of life.[E4] Sometimes, admitting a patient for a few days for education and intensive topical therapy can be helpful and can allow exploration of adherence to an agreed on treatment plan. Furthermore, skin infection, particularly with *Staphylococcus aureus* and, less commonly, herpes simplex, can be main drivers of disease flares. Therefore it is important to be vigilant during physical examination and to identify and treat skin infections when present. It is accepted practice to also use antimicrobial soap replacement in such situations, but there is only limited evidence that regular antimicrobial therapy (eg, antimicrobial bath additives) as a prophylactic measure reduces the risk of disease flares.[E5] In young children occlusive garments (wet wraps) are commonly used as a short-term therapy to reduce more generalized eczematous inflammation, and some centers also use them for long-term treatment of severe cases. However, there is limited randomized controlled trial (RCT) evidence; long-term studies that evaluate systemic absorption and skin atrophy are lacking, and the use of such garments is rather impractical in adults.[E6]

With regard to immunosuppressive treatments, there is a paucity of published evidence to guide clinical practice, especially in children, and therefore prescribing has to be guided by experience in adults and the use of these drugs in patients with other severe childhood inflammatory disorders, such as rheumatoid arthritis or inflammatory bowel disease.[E7] Therefore, not surprisingly, there is wide variation in treatment approaches among clinicians, as suggested by a recent survey among pediatric dermatologists in 8 European countries.[E8] In this survey cyclosporine was the most used agent overall for treatment periods up to a year, whereas azathioprine and especially methotrexate are instituted less frequently but for longer treatment courses. Oral glucocorticosteroids are not recommended for long-term treatment because of the risk of diabetes, hypertension, gastric ulcers, osteoporosis, skin atrophy, and, in children, detrimental effects on growth.[E9] A complicating factor is that systemic immunosuppressive drugs are not licensed for use in patients with severe AD, except cyclosporine, which is licensed for patients older than 18 years of age in many countries. There is no officially agreed on minimum age for the use of immunosuppressive therapy in children, and such considerations are, to a degree, arbitrary. Many physicians only use such agents in teenagers rather than younger children, but this is not based on robust evidence, and research with regard to drug safety in younger children and optimal dosing to maximize efficacy and minimize toxicity is clearly needed.[E7]

Furthermore, which systemic agent is preferred as a first-line therapy varies and depends not only on licensing considerations but also on the individual clinical situation. For instance, where disease control needs to be achieved quickly, cyclosporine would be the drug of choice. However, it is considered less suitable for long-term therapy because of its side effect profile. In such situations treatment with either azathioprine or methotrexate could be preferable.

Cyclosporine

Cyclosporine is a potent inhibitor of T lymphocyte–dependent immune responses. A systematic review of 11 clinical trials suggested that it is an efficacious treatment but that relapse is rapid once therapy is discontinued.[E10] The effectiveness of cyclosporine was similar in children and adults, with better tolerability seen in younger patients. If cyclosporine is effective, remission is commonly seen within a few weeks. However, potential nephrotoxicity and hypertension limit its long-term use, and regular blood pressure and renal function measurements are therefore important. See Boxes E1 and E2 for monitoring considerations for the use of systemic immunosuppressants.

Azathioprine

Azathioprine inhibits purine synthesis and thus proliferation of leukocytes. The target cells and mechanism of action in AD are not fully elucidated.[E11] Azathioprine has a complex metabolism with several immunosuppressant metabolites. The balance between thiopurine metabolites is governed by thiopurine methyltransferase (TPMT) activity, and the pretreatment determination of TPMT genotype or activity level allows informed drug dosing to minimize myelotoxicity. Other side effects include headache and gastrointestinal upset, hepatotoxicity, and drug hypersensitivity. There is concern about the potential long-term risk of lymphoma based on observations in patients with inflammatory bowel disease, but the risk increase seen might be related to inflammatory bowel disease itself rather than drug related.[E12] More recently, the emergence of progressive multifocal leukoencephalopathy (PML) in patients treated with azathioprine, either in combination with other immunomodulators or as a single agent, has given further pause regarding this agent. A large-scale ecological study of reported cases of PML in patients receiving

immune suppression suggests that azathioprine appears to confer a significantly higher risk of PML compared with cyclosporine (lower risk) or methotrexate (minimal risk). These risks might be most relevant in the context of autoimmune disease and, to the best of our knowledge, have not been reported in patients with AD.[E13] Azathioprine has a slow onset of action, with clinical improvement sometimes only seen 8 weeks into therapy. Two double-blind, placebo-controlled trials in adults with severe AD reported significant improvement in disease severity and quality of life.[E2,E9] More recently, an RCT comparing azathioprine and methotrexate in adults with severe AD suggested comparable efficacy, but this trial (n = 42) was not adequately powered to demonstrate efficacy equivalence between the 2 drugs.[E14]

Methotrexate

As with azathioprine, the mechanism of action of methotrexate in patients with AD is not fully understood, but it is known to have anti-inflammatory properties and to also reduce allergen-specific T-cell activity.[E1] Gastrointestinal disturbance, in particular nausea, liver function abnormalities, and bone marrow suppression, are potential side effects, but the medication is generally well tolerated and considered safe in the long-term, partly based on rheumatologic experience in children and adults. Onset of action is equally slow, as seen with azathioprine. Subcutaneous administration can improve bioavailability and tolerability in patients who have either not responded to treatment or who have significant gastrointestinal intolerance. In addition to the RCT that compared methotrexate with azathioprine in adults, there has been one recent RCT in children (n = 40) comparing methotrexate with cyclosporine, also suggesting equal treatment responses.[E15]

Other systemic treatments for severe AD

Because no systemic treatment is universally safe and effective, several other systemic treatments have been tried over the years for recalcitrant AD. These include IFN-γ, mycophenolate mofetil, intravenous immunoglobulin, and omalizumab (an IgE mAb).[E15] The evidence base for these treatments rests on case series or small open trials and is not sufficiently robust to guide clinical practice.[E1] Chinese herbal therapies, which showed early promise more than a decade ago, have since failed to gain a license in the European Union, United States, or Japan.

THE CASE REVISITED

Our patient with severe AD was treated with the 3 most commonly used systemic immunosuppressants only to eventually respond to methotrexate. We emphasize that this is an illustrative case to exemplify one child's treatment course and should not be interpreted as a comparative study or validated evidence on which to base therapeutic decisions. Given the significant effect on a patient's quality of life and associated comorbidities, the current paucity of clinical trial evidence and new drug developments, particularly in children, are frustrating but equally understandable. Conducting drug trials in children is generally difficult because of licensing and safety issues. In addition, severe AD is a complex multiphase disease involving skin barrier impairment and multiple immunologic pathways in the skin and systemically. The disease typically follows a waning and waxing pattern and is often compounded by skin infection. Small numbers of patient with severe disease attending single centers make the disease financially less lucrative for the development of new drugs. Furthermore, the small case series that have reported on the use of biologic agents in patients with AD have shown limited effect on disease activity.[E16]

The current state of affairs should not stop us from conducting clinical trials of existing agents. A good example of what can be done in a pediatric disease is acute lymphoblastic leukemia. A series of 4 clinical trials conducted by the UK Medical Research Council demonstrated an increase in 12-year survival from 64% to 83% achieved through maximizing the efficacy and safety of existing therapies rather than the development of new drugs.[E17] However, acute lymphoblastic leukemia had the benefit of good phenotyping; well-defined outcome measures, including biomarkers; and a high priority for research funding. From that point of view, we are moving forward in the right direction in AD research. For instance, the discovery of filaggrin loss-of-function mutations has provided an important genetic marker that might well influence therapeutic responses to systemic treatments, and this needs to be assessed in clinical trials. It will also be important to study whether any systemic immunosuppressive agents alter the cytokine signatures of known T- and B-cell subsets both locally in the skin and systemically. As our understanding of the complex immunology of AD improves, new systemic drug targets might become available. Last but not least, further lessons regarding long-term side effects can be learned from solid organ transplant recipients, rheumatology, and gastroenterology, as well as patient registries.

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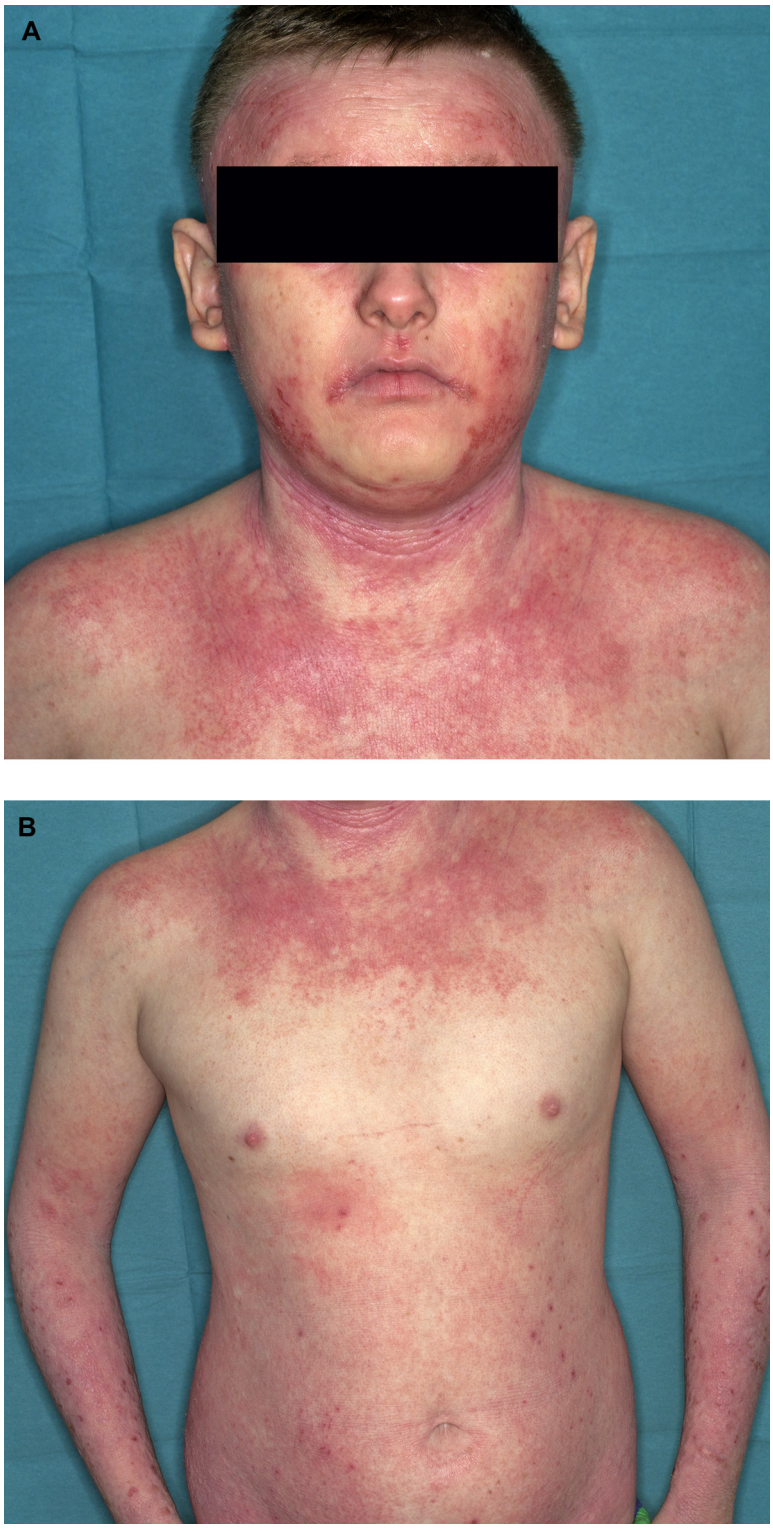

FIG E1. **A** and **B,** Severe AD can have a significant effect on the lives of patients. Despite potent topical and antimicrobial treatment, this 12-year-old had extensive AD. His symptoms finally got better on methotrexate, having previously not responded to cyclosporine and azathioprine.

Box E1. Suggestions for baseline pretreatment screening and other considerations for systemic immunosuppressant treatment in patients with AD

1. Pretreatment infection screening can include varicella zoster virus immune status, viral hepatitis screening, Mantoux/ImmunoSpot tuberculosis screening, HIV status, and possibly human herpesvirus 8 status, all depending on the population being treated. This requires local interpretation.
2. Pregnancy prevention should be considered, when appropriate. US Food and Drug Administration pregnancy categories are as follows: cyclosporin C, azathioprine D, mycophenolate mofetil D, and methotrexate X. This is relevant for any potentially pregnant patient and should be understood by the prescriber, the patient, and her family, if relevant.
3. Live vaccines (eg, measles, mumps, rubella; yellow fever; typhoid; and smallpox) are contraindicated while taking cyclosporine, methotrexate, and azathioprine.
4. Killed vaccines (eg, influenza, hepatitis A, polio, and rabies) might be less likely to induce immunization in immunosuppressed patients.
5. Immunosuppressed patients might have more severe forms of infection, such as influenza, and killed vaccines are therefore advised in patients receiving these therapies. Annual influenza vaccine is recommended.
6. Pneumococcus vaccines are recommended approximately every 5 years, as guided by relevant antibody titers.
7. Patients and parents should be educated on sun behaviors while receiving immunosuppressants because of an increased risk of skin cancer.
8. Vitamin D levels should be checked before and during immunosuppressant treatments and supplemented as necessary. Careful sun avoidance is widely recommended in immunosuppressed patients. Vitamin D deficiency is common in northern climates and will be exacerbated by active sun avoidance.
9. Each treatment has individual screening protocols for renal, hepatic, and bone marrow impairment, and prescribers need to be familiar with these (see Box E2).

Box E2. Drug-monitoring considerations for cyclosporine, azathioprine, and methotrexate

Current monitoring practice varies between countries and centers and in children is primarily based on experience from other diseases, such as inflammatory bowel disease and rheumatoid arthritis. There are no official prescribing guidelines for the use of systemic therapies in children or adults with AD. It is good practice to monitor treatment response with validated severity scores.

CYCLOSPORINE

Dose: Initially 2.5 mg/kg daily, increase to maximum of 5 mg/kg daily in exceptional circumstances.

Drug monitoring: Full blood count, renal and liver profile, as well as blood pressure at baseline, then fortnightly for first 2 months, and then at least every 3 months.

AZATHIOPRINE

Dose: Initially 1 mg/kg/d, increase to maximum of 3 mg/kg/d, taking account of TPMT result TPMT <3 nmol/h/mL – contraindicated, TPMT 3-8 nmol/h/mL – low dose 0.5-1 mg/kg/day, TPMT 8-14.5 nmol/h/mL 1-3 mg/kg/day, TPMT >14.5 nmol/h/mL consider >3 mg/kg/day if no response.

Drug monitoring: Full blood count, renal and liver profile, and TPMT levels at baseline, then weekly for first month, and then once every 3 months. Increases in dose should be accompanied by weekly blood tests. Repeat blood count if severe throat infection or other signs of potential marrow suppression.

METHOTREXATE

Dose: Initially 200 μg/kg once weekly increased to a maximum of 400 μg/kg once weekly, depending on response. Test dose is usually given at start of therapy, followed by blood a week later. The subcutaneous route can be used if the oral route is ineffective or nausea is severe. Folic acid is given at least once weekly in conjunction with methotrexate (5 mg weekly on a different day). However, folic acid regimens vary, and evidence is not conclusive as to which is most efficacious.

Drug monitoring: Full blood count, renal and liver profile, chest radiograph, procollagen III (only in adults because unreliable in growing children) at baseline and then fortnightly for the first month and at this frequency after each dose change.

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